# Synthesis and Properties of Biodegradable Segmented Poly-ε-caprolactone

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Received 1 May 2013; Accepted 23 Oct 2013; doi: 10.5405/jmbe.1534

**Abstract**

Block copolymers have been used to tune the chemical and physical properties of degradable materials for tissue engineering. In this study, a series of urethane linkages containing segmented poly-ε-caprolactone (sPCL) with various block lengths and weight ratios were synthesized and characterized. The molecular conformations and characteristics of sPCL were investigated using nuclear magnetic resonance, Fourier transform-infrared spectroscopy, and gel permeation chromatography. The effects of the molar ratio and molecular weight of ε-caprolactone precursors on the mechanical properties were studied. The results show that the tensile strength of sPCL, which is tunable, was 35 MPa, much higher than that of a typical PCL sample (16 MPa). In addition, it was found that increasing the number of urethane linkages improves elongation. *In vitro* studies confirmed that the change of molecular weight of sPCL was significantly accelerated compared to that of homopolymers. These results suggest that sPCL has potential as a tailorable material for implantable devices.

***Keywords***: Segmented poly-ε-caprolactone, Degradation, Copolymer, Urethane

## 1. Introduction

Bioresorbable polymers such as polylactide (PLA), polyglycolide (PGA), poly-3-hydroxybutyrate (PHB), poly (ε-caprolactone) (PCL), and their copolymers are used extensively in tissue engineering [1-4]. For implant applications, these synthetic polymers offer good biocompatibility, process stability, and tunable rates of biodegradation and mechanical strength. For instance, functional groups can be added to tune the polymer physico-mechanical properties for medical applications. Block and random copolymers can also be formed using monomers such as polyethylene glycol (PEG) or ethylene oxide.

PCL, a well known degradable aliphatic polyester, is biocompatible and biodegradable due to the enzymatic and pH-dependent breakdown of ester bonds. Unlike PLA and PGA, which degrade into acidic substances, PCL has less acidic degradation products and a nontoxic nature, making it more suitable for implants and drug delivery [5-7]. PCL has been reported to cause a rather mild inflammatory host response [8]. However, owing to its high hydrophobicity and remarkable degree of crystallinity, a slow diffusion rate of water and a long hydrolytic bulk degradation period of up to 2~4 years has limited its clinical use [5,9]. Although various modification techniques have been demonstrated by *in vitro* and *in vivo* studies, the lack of elasticity and an unpredictable degradation period need to be overcome.

For potential implant applications, it is highly desirable to fine tune a material's mechanical behavior and degradation period. Various copolymer and polymer blends of PCL have been prepared, including those with ethylene oxide [10], lactide [11-15], lysine [16], and polysaccharides [17,18], to enhance its mechanical performance and increase degradation time [19,20]. Cohn *et al*. synthesized a series of PLA-PCL-PLA tri-block couplings with hexamethylene diisocynate (HDI) as the chain extender. Superior flexibility and adjustable mechanical strength as the length of PLA block changed were observed. In addition, poly (ethylene oxide) (PEO) has been used to develop multiblocks such as PCL/PEO to tailor the degree of hydrophilicity and the degradation rate [21,22]. Recently, new linkers have been introduced into the PCL main chain to control degradation. Pukkinen *et al*. synthesized oxazoline-linked PCL with a diverse range of molecular weights of the PCL precursors [23]. It was demonstrated that the erosion rate can be improved by tailoring the PCL block length.

The present study synthesizes segmented PCL (sPCL) with various weight ratios and block lengths of PCL precursors. Following one-shot synthesis, a family of degradable sPCL were obtained and studied. The effect of copolymer block composition on the physical properties of sPCL was investigated. Furthermore, the effects of PCL segment length

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on the crystallinity and *in vitro* degradation characteristics of sPCL were also examined.

## 2. Experimental design

### *2.1 Materials*

PCL (Mw 89639), as PCL diols with molecular weights of 530 (PCL530), 2000 (PCL2000), and 10000 (PCL10000), 4,4-methylenebis(cyclohexyl isocyanate) ($H_{12}$MDI), dibutyltin dilaurate ($T_{12}$), and dimethyl-$d_6$-sulfoxide (DMSO-$d_6$) were purchased from Aldrich (Aldrich Chem. Co., WI, USA). All of these chemicals were used as received. Dimethylacetamide (DMAc), ethyl ether, and ethyl alcohol were purchased from Fluka (Fluka Co., USA). All solvents were high-performance liquid chromatography (HPLC) grade.

### *2.2 Preparation of segmented poly-ε-caprolactone*

The synthesis of sPCL was as follows, using PCL10000: PCL530 = 75:25 (weight ratio) as an example. PCL10000 (75 g) was dissolved in 58.5 g of DMAc and placed in a two-necked round-bottomed flask. Then, 14.3 g of $H_{12}$MDI and 60 mg of $T_{12}$ (as the catalyst) were added and mixed. After the mixture had been vigorously stirred and reacted at 60 ℃ for a predetermined time, PCL530 (25 g) dissolved in 58.5 g of DMAc was injected at a rate of 2 ml/min with a syringe into a reactor equipped with mechanical stirring. The reaction was carried out for 8 h under stirring and extra amounts of $H_{12}$MDI, DMAc, and $T_{12}$ (4.3 g, 117 g, and 340 mg, respectively) were added into the reactor.

Then, 0.2 g of butylamine was added to the resulting polymer to consume excess diisocynates and terminate the reaction. The resulting sPCL resin was purified by a precipitation polymer with 25 ℃ water for 4 h to remove DMAc. Finally, sPCL was extracted twice using the Soxhlet method with ethanol and diethyl ether for 8 h at 90 ℃. The products were dried under vacuum for 24 h and kept under vacuum. The purification processes were repeated several times to remove impurities once the relative toxicity of the sPCL was found by the MTT assay. The final purified sPCL resin was then examined and found to exhibit no cytotoxicity for further *in vitro* and *in vivo* studies.

### *2.3 Characterization*

$^{1}$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded with a 500 MHz Varian Unity Inova (Varian Inc., CA, USA) high-resolution NMR spectrophotometer. All spectra were obtained at 85 ℃ from a sample dissolved in DMSO-$d_6$ in 5-mm NMR tubes. The composition and chemical structure of PCL and sPCL were thus determined.

Molecular weights (Mw, Mn) and the molecular weight distribution were determined using gel permeation chromatography (GPC) with a Waters 515 HPLC Pump and a Waters 2414 Refractive Index Detector (Waters Instrument, MA) equipped with a series of columns (KF-801, KF-802, and KF-803, Shodex, NY). DMAc at a 1 ml/min flow rate was the mobile phase. The resulting polymers were dissolved in DMAc (0.5 wt%), and 100 μl of the resulting solution was injected at 70 ℃. PEO/PEG standards with molecular weights of 615 to 116,300 were used for the calibration.

### *2.4 Mechanical properties*

Samples used for mechanical testing were cut into dumbbell-shaped specimens. Tensile and elongation strength tests following ASTM D638 were performed using a universal material testing machine (Instron Model 4467, Instron, MA) equipped with a maximum 500-N load cell. The tests were run at an extension rate of 150 mm/min. Three specimens per sample were tested.

### *2.5 In vitro degradation*

The *in vitro* degradation of PCL and sPCL was determined in accordance with the ISO 10993-9 standard. Samples were cut to a size of 2.0 cm × 5.0 cm × 0.5 mm (thickness). The testing specimens were dried and placed in a dry box (25 ℃/40% relative humidity) for 48 h prior to study. The samples were submerged in a 50-ml round-bottomed flask containing 15 ml of phosphate-buffered saline (PBS, at pH 7.4) with a sealed joint. The sealed flasks were maintained at 37 ± 1 ℃ in a shaking incubator at 100 rpm for 10 weeks. Testing pieces were removed from the solution to sample and monitor the molecular weight changes by GPC weekly.

## 3. Results and discussion

### *3.1 Synthesis strategy of segmented poly- ε -caprolactone*

A series of sPCL copolymers with various segment lengths and block compositions were polymerized using $H_{12}$MDI as the coupling agent. The progress of sPCL synthesis was monitored with GPC. As shown in Table 1, the polydispersity of the $H_{12}$MDI-coupled polymer was mostly 2 to 2.6 with the measured molecular weight (Mn) ranging from 30000 to 54000. The reaction for sPCL was conducted as schematically described in Fig. 1. The synthesis strategy is based on $H_{12}$MDI reacting with OH-terminated PCLs with various segment lengths to form urethane linkages along the copolymer backbone. Several successful attempts were made to synthesize sPCL, including PCL530/PCL2000 (ratios of 25/75, 50/50, and 75/25), PCL530/PCL10000 (ratios of 25/75, 50/50, and 75/25), PCL530 (100%), PCL2000 (100%), PCL10000 (100%), and a PCL homopolymer, without any coupling agent. The flexible urethane linkages and composition of PCL segments determine the crystallinity and mechanical properties, and thus affect biodegradability.

### *3.2 Polymer characterization*

sPCL copolymers generated by reacting PCL blocks with various lengths with $H_{12}$MDI were studied by NMR. $^{1}$H and $^{13}$C NMR data are shown in Fig. 2. Figure 2(a) shows the chemical structure of PCL polymers. The symbols above the structure refer to $^{1}$HNMR signals in (b) and $^{13}$C NMR signals in (c). Typical resonances of selected PCL diols were at 3.9~4.1 ($\delta H^{a+n}$), 1.4-1.6 ($\delta H^{b+d,k+l}$), and 2.2-2.3 ($\delta H^{b+d,k+l}$). Additionally,

Table 1. Molecular weights and crystallinity of synthesized sPCL.

| Polymers | | | | Molecular Weight (g/mol) | | | Crystallinity (%) |
|---|---|---|---|---|---|---|---|
| Composition | Ratio (%) | | | Mn | Mw | Mw/Mn | |
| | $PCL_{530}$ | $PCL_{2000}$ | $PCL_{10000}$ | | | | |
| PCL Homopolymer (Control group) | - | - | - | 54426 | 79964 | 1.5 | 60.3 |
| $PCL_{530}$ | 100 | - | 30117 | 40910 | 60050 | 2.0 | 31.4 |
| $PCL_{2000}$ | - | 100 | - | 40910 | 84012 | 2.1 | 48.0 |
| $PCL_{10000}$ | - | - | 100 | 42793 | 89536 | 2.1 | 42.7 |
| $PCL_{530}/PCL_{2000}$ | 25 | 75 | - | 33907 | 81377 | 2.4 | Amorphous |
| $PCL_{530}/PCL_{2000}$ | 50 | 50 | - | 38639 | 96598 | 2.5 | Amorphous |
| $PCL_{530}/PCL_{2000}$ | 75 | 25 | - | 40551 | 85157 | 2.1 | Amorphous |
| $PCL_{530}/PCL_{10000}$ | 25 | - | 75 | 42893 | 111523 | 2.6 | 44.8 |
| $PCL_{530}/PCL_{10000}$ | 50 | - | 50 | 35133 | 84320 | 2.4 | 17.7 |
| $PCL_{530}/PCL_{10000}$ | 75 | - | 25 | 36985 | 88764 | 2.4 | Amorphous |

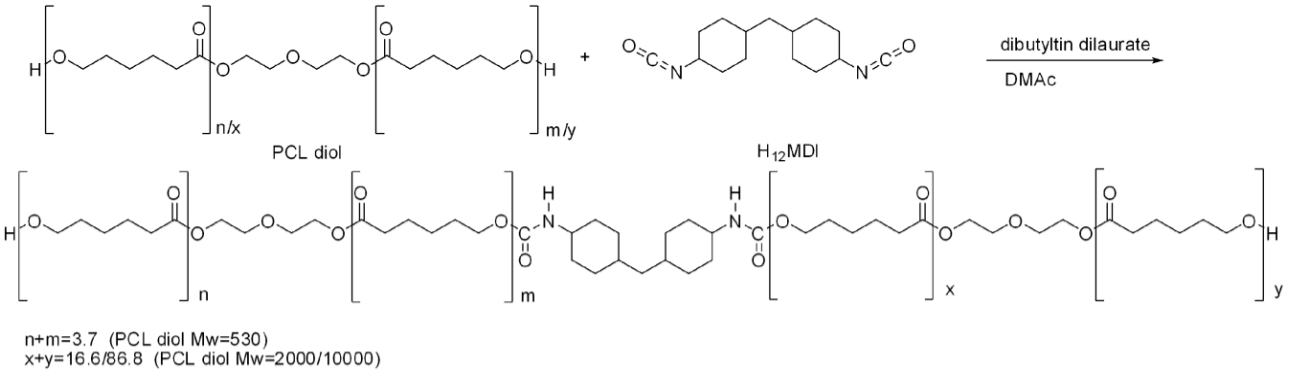


Figure 1. Synthesis of sPCL using various ratios and molecular weights of PCL diols.

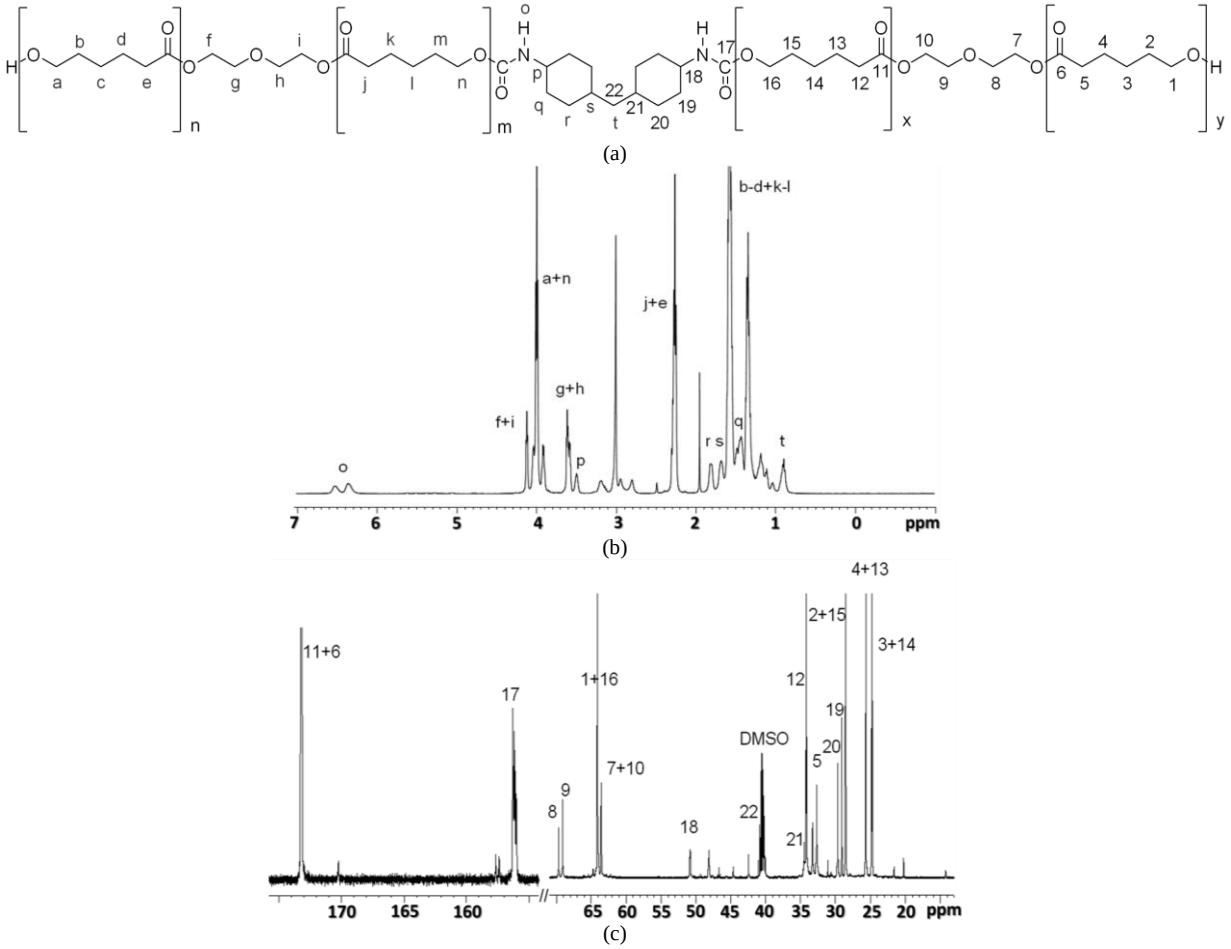


Figure 2. (a) Structure of sPCL. (b) $^{1}$HNMR signals and (c) $^{13}$CNMR signals.

peaks were found at 3.5 (δ $H^p$), 1.4 (δ $H^q$), 1.8 (δ $H^r$), 1.7 (δ $H^s$), and 0.9 (δ $H^t$) due to the coupling agent $H_{12}$MDI. The formation of the urethane groups was detected at 6.3~6.6 (δ $H^o$). In the $^{13}$C NMR spectra (Fig. 2(c)), the peaks of PCL diols and $H_{12}$MDI are in the 24~70 ppm range, and the resonances of –COO of the urethane group and PCL are at 156 and 173 ppm, respectively. These peak assignments reveal that urethane-linked sPCL was successfully synthesized. In addition, differential scanning calorimetry was used to characterize the crystallinity (C), which was calculated as:

$$C = \Delta H/(wPCL \times \Delta Href) \quad (1)$$

where wPCL is the weight fraction of PCL in the copolymer, ΔH is the enthalpy of fusion measured at the melting point, and ΔHref (136.1 J/g) is the reference melting enthalpy of 100% crystalline PCL.

Homogeneous PCL, with a crystallinity of 55-60%, is a typical semi-crystalline aliphatic polyester. From our calculations, as shown in Table 1, it fell at 60.3%. For PCL synthesis using coupling polymerization, the coupling agent $H_{12}$MDI interferes with PCL crystallization, decreasing the crystallinity to 31.4%. The data also reveal that sPCL (PCL530/PCL2000) exhibited at even lower degree of crystallinity, up till amorphous.

The Fourier transform-infrared spectra (data not shown) of two representative polymers, homopolymer PCL and sPCL, displayed a typical peak at around 1730 $cm^{-1}$, attributed to the stretching vibration of C = O in PCL. In addition, the sPCL spectra displayed the peaks of amide (NH) stretching absorption at around 3363 $cm^{-1}$ and hydrogen-bonded NH stretching absorption at around 1550 $cm^{-1}$, which correspond to the urethane linkages.

The mechanical properties of sPCL were measured and compared to those of homogeneous PCL dumbbell-shaped samples obtained using the same fabrication method. The tensile strength of these polymers is shown in Fig. 3. It is apparent from the data that the molecular weight and ratio of PCL segments plays an important role in determining the mechanical behavior of the copolymer. Of note, sPCL (PCL530/PCL10000, ratio 25/75) exhibited a remarkably high tensile strength of 36 MPa, much higher than that of the homopolymer (16 MPa). However, both sPCL (PCL530/PCL10000, ratio 25/75) and the PCL homopolymer displayed similar crystallinaties of around 44%. The superior tensile strength of sPCL may be due to the urethane linkages in the polymer chains and consequent powerful hydrogen bonds [24-26]. These inter-molecular hydrogen bonds increase the force among long, aligned polymer chains. As a result, the tensile strength doubled. However, the tensile strength of sPCL (PCL530/PCL10000, ratio 75/25) is only slightly above 10 MPa. It was found that amorphous sPCL formed when the copolymer had many short PCL segments. The poor mechanical properties obtained with a high number of short PCL segments can be attributed to the amorphous nature of the resulting structure.

As shown in Fig. 4, typical elongation at break values of PCL and PCL530/PCL2000 (ratio 75/25) were 620% and 1175%, respectively. The enhanced elasticity of sPCL may be due to the hard segment domains, which consist of coupling agent $H_{12}$MDI and low-molecular-weight PCL diols. The strong inter-molecular hydrogen bonding enhanced the mechanical properties, similar to strong non-covalent crosslinking [24-26]. Segmented copolymer therefore had tendency of tailoring the molecular chains back to the initial molecule alignments. The enhanced flexibility of the copolymers can be attributed to the urethane linkages.

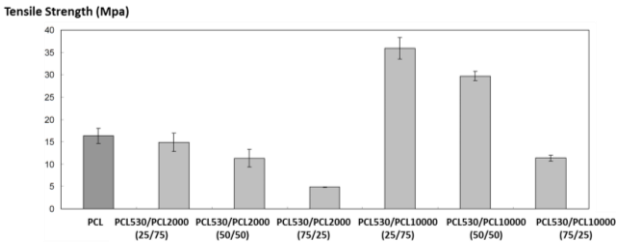


Figure 3. Tensile properties of homopolymer PCL and various types of segmented PCL

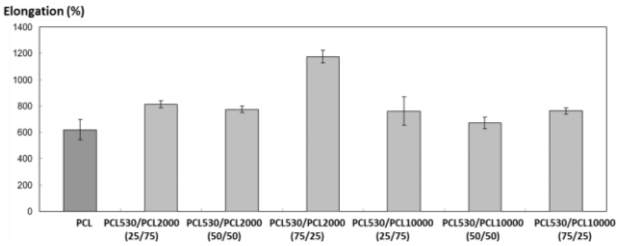


Figure 4. Elongation at break values of PCL homopolymer and sPCL prepared with various molecular weights and ratios of PCL blocks.

### *3.3 In vitro degradation*

Figure 5 summarizes the effect of varying the length of PCL blocks, with PCL530/PCL2000 (25/75), PCL530/PCL10000 (25/75), and PCL, on biodegradability. Casting films were cut and incubated *in vitro* at 37 ℃. Cohn *et al.* reported that additional PLA blocks introduced into PCL sequences affected the *in vitro* weight loss rate of the polymer [22]. It was suggested that a shorter PLA block prevents PCL from crystallizing, making it degrade more rapidly. The degree of crystallinity of copolymers increases with segment length. Here,. The variation of weight loss, as shown in Fig. 5, reflects the trend that with shorter segments, more urethane linkages form, increasing weight loss. The PCL homopolymer partially degraded (47.17 ± 6.8%) at the $10^{th}$ week, whereas the amorphous PCL530/PCL2000 (25/75) film with a short block length approached 79.29 ± 4.3% weight loss. These results indicate that the higher weight loss rate may be due to the introduction of urethane linkages, which affect PCL crystallizability by causing the growth of amorphous regions. It has been suggested that during the degradation process of the PCL matrix, the degradation mainly starts from amorphous regions in an aqueous environment. This involves water diffusing into the loosely packed amorphous areas, a simple ester hydrolysis, and degradation products that are metabolized into carbon dioxide and water [27,28]. After most amorphous regions have been degraded, the hydrolysis slowly moves toward the center of the crystalline domain. Thus weight loss

results here apparently show similar effect of low crystallinity toward fast rate of degradation owing to the short blocks length.

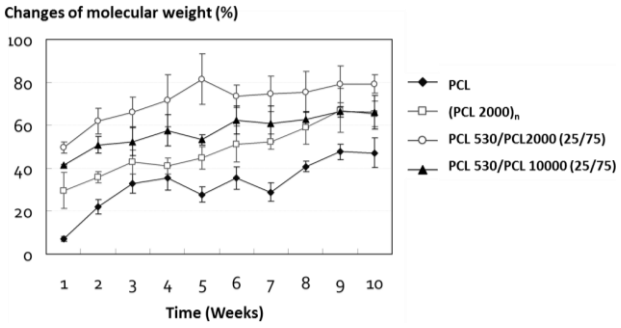


Figure 5. *In vitro* degradation profiles of PCL and sPCL. Changes of molecular weight are shown as a function of degradation time.

## 4. Conclusion

A strategy for synthesizing urethane-linked biodegradable PCL with tailored mechanical properties and a fast hydrolytic degradation process was proposed. sPCL with urethane linkages introduced into the polymer chain exhibited high flexibility (elongation of up to 1200%), remarkable tensile strength (above 200%), and a significant changes of molecular weight. By tailoring the ratio of linkages within different lengths of PCL blocks, the obtained sPCL had excellent mechanical properties and a fast degradation rate. Our results reveal that urethane-linked PCL has potential as a tunable material for medical applications. A similar strategy could be used to alter the material characteristics of PLA, PGA, and PLGA.

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